| FORM PTO-1449/A and B (modified PTO/SB/08) | APPLICATION NO.: 10/667,931     | ATTY. DOCKET NO.: N0469.70022US02 |  |
|--|---------------------------------|-----------------------------------|--|
| INFORMATION DISCLOSURE                     | FILING DATE: September 22, 2003 | CONFIRMATION NO.: 1625            |  |
| STATEMENT BY APPLICANT                     | APPLICANT: Poh K. Hui           |                                   |  |
|  | GROUP ART UNIT: 1625            | EXAMINER: Gollamudi S. Kishore    |  |

U.S. PATENT DOCUMENTS

| Examiner's | Cite | U.S. Patent Document |              | Name of Patentee or Applicant of Cited | Date of Publication or Issue    |  |
|------------|------|----------------------|--------------|--|---------------------------------|--|
| Initials # | No.  | Number               | Kind<br>Code | Document Document                      | of Cited Document<br>MM-DD-YYYY |  |
|            |      | 3,945,956            |              | Garner                                 | 03-23-1976                      |  |
|            |      | 4,515,736            |              | Deamer                                 | 05-07-1985                      |  |
|            |      | 4,636,381            |              | Takada et al.                          | 01-13-1987                      |  |
|            |      | 4,646,756            |              | Watmough et al.                        | 03-03-1987                      |  |
|            |      | 4,680,171            |              | Shell                                  | 07-14-1987                      |  |
|            |      | 4,683,092            |              | Tsang                                  | 07-28-1987                      |  |
|            |      | 4,722,943            |              | Melber et al.                          | 02-02-1988                      |  |
|            |      | 4,748,216            |              | Tom                                    | 05-31-1998                      |  |
|            |      | 4,753,788            |              | Gamble                                 | 06-28-1988                      |  |
|            |      | 4,880,635            |              | Janoff et al.                          | 11-14-1989                      |  |
|            |      | 4,946,787            |              | Eppstein et al.                        | 08-07-1990                      |  |
|            |      | 4,957,656            |              | Cerny et al.                           | 09-18-1990                      |  |
|            |      | 4,978,483            |              | Redding, Jr.                           | 12-18-1990                      |  |
|            |      | 5,006,343            |              | Benson et al.                          | 04-09-1991                      |  |
|            |      | 5,089,181            |              | Hauser                                 | 02-18-1992                      |  |
|            |      | 5,091,188            |              | Haynes                                 | 02-25-1992                      |  |
|            |      | 5,100,662            |              | Bolcsak et al.                         | 03-31-1992                      |  |
|            |      | 5,171,577            |              | Griat et al.                           | 12-15-1992                      |  |
|            |      | 5,171,678            |              | Behr et al.                            | 12-15-1992                      |  |
|            |      | 5,205,287            |              | Erbel et al.                           | 04-27-1993                      |  |
|            |      | 5,246,707            |              | Haynes                                 | 09-21-1993                      |  |
|            |      | 5,264,618            |              | Felgner et al.                         | 11-23-1993                      |  |
|            |      | 5,279,833            |              | Rose                                   | 01-18-1994                      |  |
|            | _    | 5,283,185            |              | Epand et al.                           | 02-01-1994                      |  |
|            |      | 5,334,761            |              | Gebeyehu et al.                        | 08-02-1994                      |  |
|            |      | 5,348,016            |              | Unger et al.                           | 09-20-1994                      |  |
|            |      | 5,695,741            |              | Schutt et al.                          | 12-09-1997                      |  |
|            |      | 5,730,954            |              | Albayrak et al.                        | 03-24-1998                      |  |
|            |      | 5,879,659            |              | Edwards et al.                         | 03-09-1999                      |  |
|            |      | 5,965,109            |              | Lohrmann                               | 10-12-1999                      |  |
|            |      | 5,368,840            |              | Unger                                  | 11-29-1994                      |  |

| EXAMINER: | DATE CONSIDERED: |
|-----------|------------------|
|           |                  |
|           |                  |
|           |                  |
|           |                  |

<sup>&</sup>lt;sup>6</sup> EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

| FORM PTO-1449/A and B (modified PTO/SB/08) |  |  | A DTO/SD/08) | APPLICATION NO.: 10/667,931                            | ATTY. DOCKET NO.: N0469.70022US02 |  |
|--|--|--|--------------|--|-----------------------------------|--|
| INFORMATION DISCLOSURE                     |  |  |              | FILING DATE: September 22, 2003 CONFIRMATION NO.: 1625 |                                   |  |
| Sheet 2 of 4                               |  |  |              | APPLICANT: Poh K. Hui                                  |                                   |  |
|  |  |  | 4            | GROUP ART UNIT: 1625                                   | EXAMINER: Gollamudi S. Kishore    |  |

## FOREIGN PATENT DOCUMENTS

|            |      |                    |                       | POREIG       | NTATENT DOCUMENTS                      |                              |                      |
|------------|------|--------------------|-----------------------|--------------|--|------------------------------|----------------------|
| Examiner's | Cite | Fe                 | oreign Patent Documer | nt           | Name of Patentee or Applicant of Cited | Date of<br>Publication of    | Translation          |
| Initials # | No.  | Office/<br>Country | Number                | Kind<br>Code | Document                               | Cited Document<br>MM-DD-YYYY | (Y/N)                |
|            |      | EP                 | 0 382 619             | A1           | Oreal                                  | 02-09-1989                   | See US<br>5,171,577* |
|            |      | EP                 | 0 561 424             | A1           | The Liposome Company, Inc.             | 09-22-1993                   |                      |
|            |      | EP                 | 0 562 641             | A1           | The Liposome Company, Inc.             | 09-29-1993                   |                      |
|            |      | EP                 | 0 957 942             | B1           | Acusphere Inc.                         | 06-16-2004                   |                      |
|            |      | JP                 | 8-151335              | A            | Otsuka Pharma Co., Ltd.                | 06-11-1996                   | Y-Claims<br>only     |
|            |      | WO                 | 89/10118              | A1           | Hemagen Pfc                            | 11-02-1989                   |                      |
|            |      | WO                 | 90/14846              | A1           | Alliance Pharma et al.                 | 12-13-1990                   |                      |
|            |      | WO                 | 91/15753              | A1           | Unger                                  | 10-17-1991                   |                      |
|            |      | WO                 | 93/09762              | A2           | Long David M Jr et al.                 | 05-27-1993                   |                      |
|            |      | wo                 | 94/028874             | A1           | Unger et al.                           | 12-22-1994                   |                      |
|            |      | WO                 | 95/12387              | A1           | Amgen Inc                              | 05-11-1995                   |                      |
|            |      | WO                 | 95/16467              | A1           | Bracco Research S.A.                   | 06-22-1995                   |                      |
|            |      | WO                 | 97/40679              | A1           | Imarx Pharmaceutical Corp              | 11-06-1997                   |                      |

<sup>\*</sup> U.S. 5,171,577 claiming same priority as EP 0 382 619

## OTHER ART - NON PATENT LITERATURE DOCUMENTS

| Examiner's<br>Initials * | Cite<br>No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | Translation<br>(Y/N) |
|--------------------------|------------|---|----------------------|
|                          |            | [No Author Listed] Division of new drug chemistry document relating to Definity. Review date, February 15, 2001.  |                      |
|                          |            | [No Author Listed] EMEA Scientific discussion relating to Sonovue. Updated until October 1, 2004. 1 page.   |                      |
|                          |            | [No Author Listed] http://www.acusphere.com/product/prod/_imagify.html.   |                      |
|                          |            | [No Author Listed] Pages from DuPont website relating to FREON. Last accessed online at<br>http://www.dupont.com/msds/40_37_2011fr.html on February 15, 2002. 5 pages.  |                      |
|                          |            | ARAI et al., Transpulmonary passage of Acrosomes®, a pressure stable, lipid based echocardiographic contrast agent: studies in pigs. J Am Coll Cardiol. 1994:23-25A. Abstract only.   |                      |
|                          |            | BOTVINICK, Stress imaging: current clinical options for the diagnosis, localization, and evaluation of coronary artery disease. Contemporary Issues Cardiol. Sept 1995;79(5):1025-57.   |                      |
|                          |            | BURN et al., Stress echocardiography. Q J med. 1995;88:755-61.  |                      |

| EXAMINER:          |    | DATE CONSIDERED: |
|--------------------|----|------------------|
| Late Britis (Life) | 1. |                  |
|                    |    |                  |
|                    |    |                  |
|                    |    |                  |

<sup>&</sup>lt;sup>#</sup> EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

| FORM PTO-1449/A and B (modified PTO/SB/08) |            |    | 4 DTCMCD (09) | APPLICATION NO.: 10/667,931     | ATTY. DOCKET NO.: N0469.70022US02 |  |
|--|------------|----|---------------|---------------------------------|-----------------------------------|--|
|  | RMATION DI |    | · ·           | FILING DATE: September 22, 2003 | CONFIRMATION NO.: 1625            |  |
|  | EMENT BY   |    |               | APPLICANT: Poh K. Hui           |                                   |  |
| Sheet                                      | 3          | of | 4             | GROUP ART UNIT: 1625            | EXAMINER: Gollamudi S. Kishore    |  |

| CHENG et al. "The Production and Evaluation of Contrast-Carrying Liposomes Made with an Automatic High Pressure System", Investigative Radiology, vol. 22, No. 1, pp. 47-55 (1987).  DE JONG et al., New ultrasound contrast agents and technological innovations, Ultrasonics, 1996 Jun;34(2-5):587-90.  GAENT/LIER et al., "Perfluoroalkylated Phosphocholines, Improved Synthesis, Surface Activity, Fluorocarbon Emulsifying Capability and Biological Properties", New Journal of Chemistry 1993, 17(5), 337-344.  Galjee, Biosis #91:493622, 1991.  GROSS, U. et al., "Phosholipid vesiculated fluorocarbons promising trend in blood substitutes" Biomat, Art. Cells & Immob. Biotech., 1992, vol. 20, (2-4) pp. 831-833.  HAYAT et al., Effects of left bundle-branch block on cardiac structure, function, perfusion, and perfusion reserve: implications for myocardial contrast echocardiography versus radionuclide perfusion imaging for the detection of coronary artery disease. Circulation, 2008 Apr 8;117(4):1832-41. Epub 2008 Mar 31. |
|---|
| DE JONG et al., New ultrasound contrast agents and technological innovations, Ultrasonics, 1996 Jun;34(2-5):587-90. GAENTZIJER et al., "Perfluoroalkylated Phosphocholines, Improved Synthesis, Surface Activity, Fluorocarbon Emulsifying Capability and Biological Properties", New Journal of Chemistry 1993, 17(5), 337-344. Galpee, Biosis #91:493622, 1991. GROSS, U. et al., "Phosholipid vesiculated fluorocarbons promising trend in blood substitutes" Biomat, Art. Cells & Immob. Biotech., 1992, vol. 20, (2-4) pp 831-833. HAYAT et al., Effects of left bundle-branch block on cardiac structure, function, perfusion, and perfusion reserve: implications for myocardial contrast echocardiography versus radionuclide perfusion imaging for the detection of coronary artery disease. Circulation. 2008 Apr   |
| Jun;34(2-5):587-90.  GAENTZLER et al., "Perfluoroalkylated Phosphocholines. Improved Synthesis, Surface Activity, Pluorocarbon Emulsifying Capability and Biological Properties", New Journal of Chemistry 1993, 17(5), 337-344.  Galjee, Biosis #91:493622, 1991.  GROSS, U. et al., "Phosholipid vesiculated fluorocarbons promising trend in blood substitutes" Biomat., Art. Cells & Immob. Biotech., 1992, vol. 20, (2-4) pp 831-833.  HAYAT et al., Effects of left bundle-branch block on cardiae structure, function, perfusion, and perfusion reserve: implications for myocardial contrast echocardiography versus radionuclide perfusion imaging for the detection of coronary artery disease. Circulation. 2008 Apr   |
| GAENTZLER et al., "Perfluoroalkylated Phosphocholines. Improved Synthesis, Surface Activity, Fluorocarbon Emulsifying Capability and Biological Properties", New Journal of Chemistry 1993, 17(5), 337-344.  Galjee, Biosis #91:493622, 1991. GROSS, U. et al., "Phosholipid vesiculated fluorocarbons promising trend in blood substitutes" Biomat. Art. Cells & Immob. Biotech., 1992, vol. 20, (2-4) pp 831-833.  HAYAT et al., Effects of left bundle-branch block on cardiac structure, function, perfusion, and perfusion reserve: implications for myocardial contrast echocardiography versus radionuclide perfusion imaging for the detection of coronary artery disease. Circulation. 2008 Apr  |
| Eluorocarbon Emulsifying Capability and Biological Properties", New Journal of Chemistry 1993, 17(5), 337-344.  Galjee, Biosis #91:493622, 1991.  GROSS, U. et al., "Phosholipid vesiculated fluorocarbons promising trend in blood substitutes" Biomat, Art. Cells & Immob. Biotech. 1992, vol. 20, (2-4) pp 831-833.  HAYAT et al., Effects of left bundle-branch block on cardiac structure, function, perfusion, and perfusion reserve: implications for myocardial contrast echocardiography versus radionuclide perfusion imaging for the detection of coronary artery disease. Circulation. 2008 Apr   |
| 17(5), 337-344.  Galjee, Biosis #91:493622, 1991.  GROSS, U, et al., "Phosholipid vesiculated fluorocarbons promising trend in blood substitutes"  Biomat, Art. Cells & Immob. Biotech., 1992, vol. 20, (2-4) pp 831-833.  HAYAT et al., Effects of left bundle-branch block on cardiac structure, function, perfusion, and perfusion reserve: implications for myocardial contrast echocardiography versus radionuclide perfusion imaging for the detection of coronary artery disease. Circulation. 2008 Apr  |
| Galjee, Biosis #91:493622, 1991. GROSS, U. et al., "Phosholipid vesiculated fluorocarbons promising trend in blood substitutes" Biomat, Art. Cells & Immob. Biotech., 1992, vol. 20, (2-4) pp 831-833. HAYAT et al., Effects of left bundle-branch block on cardiac structure, function, perfusion, and perfusion reserve: implications for myocardial contrast echocardiography versus radionuclide perfusion imaging for the detection of coronary artery disease. Circulation. 2008 Apr  |
| GROSS, U, et al., "Phosbolipid vesiculated fluorocarbons promising trend in blood substitutes" Biomat., Art. Cells & Immob. Biotech., 1992, vol. 20, (2-4) pp 831-833.  HAYAT et al., Effects of left bundle-branch block on cardiac structure, function, perfusion, and perfusion reserve: implications for myocardial contrast echocardiography versus radionuclide perfusion imaging for the detection of coronary artery disease. Circulation. 2008 Apr   |
| Biomat, Art. Cells & Immob. Biotech., 1992, vol. 20, (2-4) pp 831-833.  HAYAT et al., Effects of left bundle-branch block on cardiac structure, function, perfusion, and perfusion reserve: implications for myocardial contrast echocardiography versus radionuclide perfusion imaging for the detection of coronary artery disease. Circulation. 2008 Apr   |
| perfusion reserve: implications for myocardial contrast echocardiography versus radionuclide perfusion imaging for the detection of coronary artery disease. Circulation. 2008 Apr  |
| radionuclide perfusion imaging for the detection of coronary artery disease. Circulation. 2008 Apr  |
|   |
| 9,117(14),1922 41 Enuls 2009 May 21   |
|   |
| KAUL, Myocardial contrast echocardiography in coronary artery disease: potential applications   |
| using venous injections of contrast. Am J Cardiol. 1995 Apr 13;75(11):61D-68D.  |
| O'KEEFE et al., Comparison of stress echocardiography and stress myocardial perfusion   |
| scintigraphy for diagnosing coronary artery disease and assessing its severity. Am J Cardiol. 1995  |
| Apr 13;75(11):25D-34D.  |
| OTIS et al., Contrast-enhanced transcranial imaging. Results of an American phase-two study.  |
| Stroke. 1995 Feb;26(2):203-9.   |
| PAPAHADJOPOULOS et al., Sterically stabilized liposomes:improvements in pharmacokinetics  |
| and antitumor therapeutic efficacy. Proc Natl Acad Sci U S A. 1991 Dec 15;88(24):11460-4.   |
| REGEN et al., Polymerized phospatidylcholine vesicles. Synthesis and characterization. J Am Chem Soc. 1982;104:791-5.   |
| RIESS, J.G., "Fluorine in our arteries," New J.Chem., XP-000990897, 1995, 19, 891-909 (English  |
| abstract).  |
| RIESS, J.G., "Introducing a new element-fluorine-into the liposomal membrane", Liposome Res.,   |
| 1995, XP-000525914, 5(3), 413-430.  |
| SANTAELLA, C. et al., "Emulsification of Fluorocarbons Using Perfluoroalkylated   |
| Giverophosphocholines as Surfactants or Co-Surfactants", New J. Chem., 1992, 16(3), 399-404.  |
| Seibyl, Biois #94:339104, 1994.   |
| SENIOR et al., RAMP-1 and RAMP-2 Investigators. Detection of coronary artery disease with   |
| perfusion stress echocardiography using a novel ultrasound imaging agent: two Phase 3   |
| international trials in comparison with radionuclide perfusion imaging. Eur J Echocardiogr. 2009  |
| Jan;10(1):26-35.  |
| SENIOR, Imagify (perflubutane polymer microspheres) injectable suspension for the assessment of   |
| coronary artery disease. Expert Rev Cardiovasc Ther. 2007 May;5(3):413-21.  |
| SHINODA, K. et al., "Colloidal Surfactants; Some Physiochemical Properties", Chapter 1, pp. 1-96,   |
| Academic Press, New York, 1963.   |
| SOLE-VIOLAN, L., "Partition Coefficients of Mixed Fluorocarbon-Hydrocarbon Compounds  |
| Between Fluorocarbons and Hexadecane. Relevance of Fluorocarbon Emulsion Stabilization", New  |
| J. Chem., 1993, 17(8,9), 581-583.   |

| EXAMINER: | DATE CONSIDERED: |
|-----------|------------------|
|           |                  |
|           |                  |

<sup>\*</sup> EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

| FORM PTO-1449/A and B (modified PTO/SB/08) |                        | APPLICATION NO.: 10/667,931 | ATTY. DOCKET NO.: N0469.70022US02 |  |                                |  |
|--|------------------------|-----------------------------|-----------------------------------|--|--------------------------------|--|
| INFORMATION DISCLOSURE                     |                        |                             |                                   | FILING DATE: September 22, 2003 CONFIRMATION NO.: 1625 |                                |  |
|  | STATEMENT BY APPLICANT |                             |                                   | APPLICANT: Poh K. Hui                                  |                                |  |
|  |                        |                             |                                   | GROUP ART UNIT: 1625                                   | EXAMINER: Gollamudi S. Kishore |  |
| Sheet                                      | t 4 of 4               |                             |                                   | GROOF ART UNIT: 1023                                   | EXAMINER: Gollamudi S. Kishore |  |

| SONNE et al., Left ventricular opacification after intravenous injection of Albunex. The effect of   |
|--|
| different administration procedures. Int J Card Imaging. 1995 Mar;11(1):47-53.                       |
| SUTHERLAND et al., "Color Doppler Myocardial Imaging: A New Technique for the Assessment             |
| of Myocardial Function", J. Am. Soc. Of Echocardiogr, 1994, 7(5), 441-458.                           |
| TREVINO, L, et al., "Incorporation of a perfluoroalkylalkane (rfrh) into the phospholipid bilayer of |
| dmpc liposomes results in greater encapsulation stability", Journal of Liposome Research, 1994,      |
| vol. 4 (2) pp 1017-1028.   |
| TSUTSUI et al., Comparison of low-mechanical index pulse sequence schemes for detecting              |
| myocardial perfusion abnormalities during vasodilator stress echocardiography. AmJ Cardiol. 2005     |
| Mar 1;95(5):565-70.  |
| Uemura, Biosis #80: 105491, 1979.  |
| Uemura, Embase, #79180131, 1979.   |
| ULENDORF, "Physics of Ultrasound Contrast Imaging: Scattering in the Linear Range", IEEE             |
| Transactions on Ultrasonics, Ferrolectrics, and Frequency Control, 1994, 41(1), 70-79.               |
| YU et al., Incremental value of parametric quantitative assessment of myocardial                     |
| perfusion by triggered Low-Power myocardial contrast echocardiography. J Am Coll                     |
| Cardiol. 2004 May 19;43(10):1807-13.   |
| ZARIF, L. et al., "Biodistribution and excretion of a mixed 4luorocarbon-hydrocarbon "dowel"         |
| emulsion as determined by 19-F NMR", Artificial Cells, Blood Substitutes, and Immobilization         |
| Biotechnology, 1994, vol. 22,(4) pp 1193-1198.   |

[NOTE—No copies of U.S. patents, published U.S. patent applications, or pending, ampublished patent applications stored in the USPD's Image File Wapper (IFW) system, are included. See 37 CFR § 1.98 and 12870GH3. Copies of all other patentiely, publications, by unpublished, pending U.S. patent applications, or other information listed are provided as required by 37 CFR § 1.98 unless J such copies were provided in an IDS in an earlier application that complies with 37 CFR § 1.98, and 2) the earlier application is relied upon for an earlier filing date under 35 U.S.C. § 1203]

| EXAMINER: | DATE CONSIDERED: |
|-----------|------------------|
|           |                  |
|           |                  |
|           |                  |

<sup>\*</sup> EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.